REMARKS

Claims 19-21, 25-29, 31, and 35-39 have been cancelled herein. Such cancellation is without prejudice on the merits to further prosecution of these claims in one or more continuing applications. Claims 18, 22-23, 30, 32-33, 40-44, and 46-53 have been amended herein. Claim 54 is newly added.

Claims 18, 22-24, 30, 32-34, and 40-54 remain in the case. Favorable reconsideration is respectfully requested.

The following remarks address the issues presented in the Office Action in the order of their appearance.

Restriction Requirement:

Applicants continue their traversal of the prior restriction requirement, while acknowledging that the same has been made final.

Applicants hereby expressly reserve their rights to rejoin the subject matter of non-elected method and process claims pursuant to the Federal Circuit Court decisions in *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 37 USPQ2d 1663 (Fed. Cir. 1996). In short, when an Applicant elects claims directed to a product, as has been done in the present case, and the product is subsequently found allowable, withdrawn process claims that depend from or otherwise include all of the limitations of the allowable product **will be rejoined**.

In light of the *In re Ochiai* and *In re Brouwer* decisions, Applicants respectfully submit with this response a set of amended claims that include both the elected product claims (as amended), as well as process claims that include all of the limitations of the elected product claims. As detailed in full hereinbelow, Applicants respectfully submit that the elected product claims are in condition for allowance. Insofar as the process claims include all of the limitations of the elected product claims, Applicants submit that all of the now-pending claims are in condition for allowance.

Sequence List:

A Substitute Sequence List (in both paper and CRF form) is submitted herewith. Applicants hereby request entry of the Substitute Sequence List attached. Also, the specification has been appropriately amended to include references to the Sequence List.

Priority Claim:

The first page of the specification has been amended to include a priority claim to the parent PCT patent application.

Abstract of the Disclosure:

An appropriate Abstract is submitted on a separate sheet, attached hereto (as required by 37 CFR §1.72(b)).

Objections to the Claims:

The objections recited in paragraphs 8-12 (at pages 4-5) of the Office Action have all been obviated either by appropriate amendment to the claims or by cancellation of the claims.

Rejection of Claims 18, 22-25, and 44-53 Under 35 USC §112, First Paragraph:

As applied to Claim 25, this rejection has been obviated by cancellation of the claim.

As applied to Claim 18, this rejection is believed to have been obviated by appropriate amendment to the claim. Specifically, Claim 18 now positively recites SEQ. ID. NOS: 1 and 2. Insofar as this rejection explicitly states that the specification is enabling for SEQ. ID. NOS: 1 and 2, the amendment to Claim 18 obviates this rejection.

As applied to Claims 24, 47, 50, and 53, this rejection is respectfully traversed. Claims 24, 47, 50, and 53, as originally submitted and as amended herein, positively

recite SEQ. ID. NOS: 1 and 2. Insofar as Office Action explicitly states that the specification is enabling for SEQ. ID. NOS: 1 and 2, this rejection is improper on its face as applied to these claims.

As applied to Claims 22-23, 44-46, 48-49, and 51-52, this rejection is respectfully traversed.

Regarding collagen-induced arthritis ("CIA") and pristane-induced arthritis (PIA) in mice, these two animal models for rheumatoid arthritis are well known in the field. Moreover, Applicants included specific reference citations to these two animal models. The Office's attention is directed to page 32 of the specification, reference numbers 23-25, and page 33 of the specification, reference numbers 31 and 34. These five references specifically address and describe the CIA and PIA mice models. In short, these two animal models for human rheumatoid arthritis are well known and the application contains explicit cites to at least five (5) prior art references describing how the models are constructed. Thus, it is submitted that these prior art animal models are sufficiently referenced in the specification to enable one of skill in the art to recreate the animal models. Lastly, as a general proposition, Applicants are encouraged to exclude from the specification that which is well known in the art; see MPEP §2164.08 and *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Because the CIA and PIA models are well known in the art, it is respectfully submitted that a detailed description of the same is not required; the citation to the relevant prior art is sufficient for sake of §112.

Moreover, and more to the point, the specification at page 12 definitively states that "Collagen arthritis (CIA) and pristane arthritis (PIA) **were induced in DBA/1 mice**..." See page 12, lines 6-7. There is no ambiguity in this statement. Further still, there is no ambiguity that the mice actually suffered from the CIA and PIA as evidenced by the very next sentence on page 12: "Mice were bled before induction of arthritis (15 animals),. **at onset of CIA (16 animals) and the onset of PIA (14 animals)**." See page 12, lines 7-9. These animals definitively exhibited CIA and PIA due to the injection of collagen and the specification states as much.

The blood taken from the animals (both before and after onset of CIA and PIA) was then tested for the presence of anti-BiP(GRP78) antibodies. See the paragraph spanning page 12, line 4, to page 13, line 3. The results of this test are presented graphically in Fig. 3. Note especially the description of Fig. 3 found at page 30, third full paragraph:

> Antibodies to recombinant human p78 in the sera of mice measured by ELISA and expressed as OD_{405}. Shown are the values for the animals bled before the induction of experimental arthritis (pre-bleed), at the onset of collagen-induced arthritis (CIA) and of pristane-induced arthritis (PIA).

In short, these mice clearly had CIA and PIA. Further still, as clearly shown by the histogram shown in Fig. 3 of the application, the CIA and PIA mice had significantly elevated levels of anti-BiP(GRP78) antibodies present in their sera. Thus, these data clearly show that animal models of arthritic exhibit increased sera titers of antibodies specific for BiP(GRP78) proteins. Thus, the specification clearly shows that the presence of antibodies specific for BiP(GRP78) is predictive of the presence of at least CIA and PIA in mice, and, by quite reasonable extension, rheumatoid arthritis in man.

Also, it appears that the passage at page 15, first full paragraph, has been misunderstood by the Office. Animals were injected with p78 first, not to induce CIA or PIA, but to determine if the pre-injection of p78 would inhibit the onset of CIA and PIA. As noted at page 15, line 10, animals were injected with 1 mg p78. One week later these animals were then immunized with type II collagen in CFA. See also the discussion that accompanies Table 2 at page 28 of the specification. As presented in Table 2, and discussed at page 15, mice pre-injected with p78 were statistically far less likely to develop CIA or PIA as compared to animals pre-injected with a saline control. The differences between the two groups were highly statistically significant. In short, the present specification amply shows that injecting a mammal with p78 inhibits the onset of arthritis in not one, but two, art-recognized *in vivo* models of rheumatoid arthritis in man (CIA and PIA in DBA/1 mice).

With regard to SEQ. ID. NOS: 1 and 2 per se, Applicants note that this rejection has been obviated in part by amending the claims to remove the phrase "or a peptide derived therefrom." As amended, the claims recite that a BiP(GRP78) protein "or a fragment thereof" is used. Applicants note that SEQ. ID. NO: 1 is 6 residues longer than SEQ. ID. NO: 2. Thus, the Office's observation that minor changes in protein sequence *might* have profound changes in functionality is not well taken. It is equally probable that large changes in protein sequence *might* have no discernible effect on biological functionality. The prior art is full of examples where fragments of full-size proteins, or truncated versions of the full-size proteins, retain the activity of the parent protein. DNA polymerase I is a good example. The full protein is a polymerase, and after cleavage by subtilisin, the large fragment (the Klenow fragment) retains its polymerase activity. This is just one example from among thousands where fragmented proteins retain the activity of the parent protein.

Also, the Rule 132 Declaration of inventor Gabriel S. Panayi, submitted herewith, contains additional objective scientific evidence showing that BiP(GRP78) proteins are conserved across species.

Specifically, after opening in paragraphs 1 and 2 by stating his familiarity with the present application (he is the first-named inventor) and his educational and professional qualifications, in paragraph 3 of his Declaration, Dr. Panayi describes an experiment showing that human mononuclear cells are stimulated by exposure to human-derived BiP(GRP78) to increase secretion of interleukin-10, while simultaneously the exposure to BiP(GRP78) causes the cells to suppress secretion of tumor necrosis factor-α.

In paragraph 4 of his Delcaration, Dr. Panayi describes a similar experiment in which human-derived BiP(GRP78) was used to stimulate mouse-derived mononuclear cells. The same results were obtained. When the mouse mononuclear cells were exposed to the human BiP(GRP78), the cells increased the production of interleukin-10.

Dr. Panayi states, in paragraph 5 of his Declaration, that these results clearly show that the biological functionality of BiP proteins is conserved across species as distant as man is from mouse. Thus, as Dr. Panayi concludes at paragraph 5 of his Declaration, BiP is likely highly conserved, both structurally and functionally, across all mammalian species.

These results are submitted to provide objective scientific evidence to rebut the Office's position that the biological data presented in the specification insufficient to support the genus "BiP(GRP78)" as presented in the claims. (See Office Action, page 7, last paragraph.) Applicants expressly traverse this portion of the Office Action and note that defining a generic term by listing a number of exemplary species that fall within the generic term is a perfectly valid and **approved** approach to defining a generic term. See MPEP §2164.08 and *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971): "How a teaching is set forth, **by specific example** or broad terminology, is not important." (Emphasis added.)

Further still, the statement at the bottom of page 7 that proteins other than SEQ. ID. NOS: 1 and 2 "would be expected to have greater differences in their activities" is irrelevant to patentability. First, the individual species within a genus of chemical compounds need not all be equally effective. See *In re Gardner*, 177 USPQ 396 (CCPA 1973). Second, Dr. Panayi's Declaration contains objective scientific evidence showing that the BiP proteins are highly conserved, functionally and structurally, across species lines. Therefore, the high variability within these proteins as suggested by the Office is not reflective of the true biological reality.

Regarding the treatment of "inflammation" per se, Applicants note that as amended the claims are directed to compositions and corresponding methods for treating rheumatoid arthritis in mammals, including man. Thus, the paragraphs in this rejection devoted to discussing treatments for "inflammation" are no longer relevant. Applicants do note, however, that there is no requirement that a patent application contain working examples in order to satisfy the first paragraph of §112. See *In re Robbins*, 166 USPQ 552 (CCPA 1970). That being said, the specification does contain

specific working examples showing that administration of BiP inhibits the onset of animal models of rheumatoid arthritis (see above). Thus, the specification clearly enables the claims as amended herein.

In light of the amendment to the claims, the above remarks, and the Rule 132 Declaration of Dr. Panayi submitted herewith, Applicants submit that this rejection has now been overcome. Withdrawal of the same is respectfully requested.

Rejection of Claims 18, 22-25, and 44-53 Under 35 USC §112, First Paragraph:

This rejection is believed to have been obviated, in part, and is, in part, respectfully traversed.

As noted above, the claims have been amended to remove the phrase "or a peptide derived therefrom." Thus, as amended, the claims recite that a BiP(GRP78) protein "or a fragment thereof" is used. Therefore, for example, SEQ. ID. NOS: 1 and 2 and fragments thereof are encompassed by the literal language of the claims. This amendment is believed to at least partially obviate this rejection.

The remainder of this rejection is traversed because BiP proteins in general, and BiP(GRP78) proteins in particular, are recognized classes of proteins to those skilled in the art. Regarding BiP proteins in general, the Examiner's attention is directed to page 4 of WO 94/08012, which was cited in the International Preliminary Examination Report. This prior art document clearly defines BiP proteins as the IgG heavy chain binding protein. This reference also notes that these proteins have a general role in associating with misfolded, unassembled, or aberrantly glycosylated proteins. The reference states that BiP is located in all eukaryotic cells within the lumen of the endoplasmic reticulum (ER). The 1994 WO reference goes on to note that BiP is a soluble protein which is retained in the ER by a receptor-mediated recycling pathway. All of this data is known in the prior art. The very phrase itself, BiP, designates a defined class of proteins known to one of skill in the art. Thus, the term BiP(GRP78) as used in the present claims is not limited solely to SEQ. ID. NOS. 1 and 2. See also

reference 17, at page 32 of the specification: Knarr et al. (1995) "BiP Binding Sequences in Antibodies," *J. Bio. Chem.* 46: 27589-27594.

Regarding native BiP(GRP78) proteins in particular, these proteins are also resident in the endoplasmic reticulum (ER) and may associate transiently with a variety of newly synthesized secretory and membrane proteins or permanently with mutant or defective proteins that are incorrectly folded, thus preventing export of the defective proteins from the ER. Native BiP(GRP78) proteins are highly conserved and are essential for cell viability. The highly conserved sequence Lys-Asp-Glu-Leu (KDEL) is present at the C-terminus of native BiP(GRP78) and other resident ER proteins, including glucose-regulated protein 94 (GRP94) and protein disulfide isomerase (PDI). See, for example, *Archives of Biochemistry and Biophysics* (1992) 296:129-136; *Hybridoma* (1995) 14(4):347-354; and *Immunity* (1997) 6:57-66.

These references show that BiP proteins in general and BiP(GRP78) proteins in particular are recognized classes of proteins to those skilled in the art. To satisfy the written description requirement of §112, Applicants are not required to provide a more stringent definition than that already understood in the art.

At the crux of this invention are 1) the previously unknown fact that there is a connection between BiP(GRP78) proteins and rheumatoid arthritis; and 2) the preparation of recombinant forms of the BiP(GRP78) proteins suitable for diagnostic and pharmaceutical use. The prior art, while describing BiP proteins in general, is completely and wholly silent regarding any connection between BiP proteins in general and rheumatoid arthritis. Insofar as BiP(GRP78) proteins are an art-recognized class of proteins, and having described two recombinant versions of this protein, and having further demonstrated that these two proteins are capable of inhibiting the onset of CIA and PIA in mice, and having demonstrated still further that BiP(GRP78) is linked to the presence of rheumatoid arthritis, it is submitted that this rejection is improper.

Withdrawal of this rejection is therefore respectfully requested.

Rejection of Claim 18 Under §102(b) in View f Ting et al., P11021, Witzmann et al., r Haas et al.:

This rejection has been obviated by incorporating the subject matter of Claim 19 into Claim 18. Claim 18 now positively recites that the immunoglobulin heavy chain binding protein as an amino acid sequence as shown in SEQ. ID. NOS: 1 or 2. Insofar as the Office has already indicated that these two sequences are free of the prior art (see page 15, paragraph 25 of the Office Action dated February 15, 2002), this rejection has been overcome.

Withdrawal of the same is now requested.

Rejection of Claim 18 Under §102(b) in View of Hsu et al.:

This rejection has been obviated by incorporating the subject matter of Claim 19 into Claim 18. Claim 18 now positively recites that the immunoglobulin heavy chain binding protein as an amino acid sequence as shown in SEQ. ID. NOS: 1 or 2. Insofar as the Office has already indicated that these two sequences are free of the prior art (see page 15, paragraph 25 of the Office Action dated February 15, 2002), this rejection has been overcome.

Withdrawal of this rejection is now requested.

Rejection of Claims 18, 22-23, and 25 Under 35 USC §102(b) in View of Kozutsumi et al.:

As applied to Claim 18, this rejection has been obviated by incorporating the subject matter of Claim 19 into Claim 18. Claim 18 now positively recites that the immunoglobulin heavy chain binding protein as an amino acid sequence as shown in SEQ. ID. NOS: 1 or 2. Insofar as the Office has already indicated that these two sequences are free of the prior art (see page 15, paragraph 25 of the Office Action dated February 15, 2002), this rejection has been obviated as to Claim 18.

The remainder of this rejection is respectfully traversed because Kozutsumi et al. fail entirely to describe a pharmaceutical composition for the treatment of any

disease state, as is recited in the present claims. First, Claim 22 as amended requires that the composition comprise an anti-rheumatoid arthritis-effective amount of "an isolated" immunoglobulin heavy chain binding protein designated BiP(GRP78). The Kozutsumi et al. reference does not, however, describe such an isolated protein. The protein used to inoculate rabbits, as discussed at page 118 of the reference, is a collagen II/GRP78 **fusion protein**, not an isolated GRP 78 protein.

Second, unwitting duplication of an invention does not result in anticipation. The Office states that Kozutsumi et al. anticipates that present pharmaceutical composition claims because Kozutsumi et al. prepared a protein in a vehicle of buffered saline and adjuvant. This, however, is improper: 1) Kozutsumi used a fusion protein, not an isolated BiP protein; and 2) Kozutsumi's formulation is not a pharmaceutical composition for the treatment of any given disease state. Kozutsumi did not prepare the inoculation as a means to treat a disease state. Kozutsumi was not treating a disease; he was inoculating rabbits to generate antibodies to a fusion protein.

Applicants agree that the intended use of a pharmaceutical composition is not given patentable weight. But in this instance Kozutsumi did not fabricate a pharmaceutical composition to treat any disease state. Kozutsumi fabricated an inoculant to raise antibodies. The two are not identical and Kozutsumi's failure to recognize his composition as a potential medicament is relevant to anticipation. To function as an anticipatory reference, the document must fully disclose the invention as claimed, including recognition of the crux of the inveniton (in this instance, the treatment of rheumatoid arthritis).

Insofar as the Kozutsumi et al. reference does not describe using an isolated BiP protein, but rather describes a collagen II/BiP fusion protein, this rejection is improper. Withdrawal of the same is now requested.

Rejection of Claims 44, 48, and 51 Under 35 USC §102(b) in View of U.S. Patent No. 5,188,964 (McGuire et al., "the '964 Patent") and Rejection of Claim 45 Under 35 USC §103 in View of the '964 Patent:

These two rejections are believed to have been obviated by appropriate amendment to Claim 44. Specifically, independent Claim 44 has been amended to recite SEQ. ID. NOS: 1 and 2. Insofar as the Office has already indicated that these two proteins are free of the prior art, this amendment is believed to render that two above-noted rejections moot.

Withdrawal of these two rejections is respectfully requested.

Rejection of Claims 44-46, 49, and 52 Under 35 USC §103 in View of the '964 Patent in Combination With Hsu et al. or Sambrook et al.:

This rejection is believed to have been obviated by appropriate amendment to Claim 44. Specifically, independent Claim 44 has been amended to recite SEQ. ID. NOS: 1 and 2. Insofar as the Office has already indicated that these two proteins are free of the prior art, this amendment is believed to render the above-noted rejection moot.

Withdrawal of this rejection is now respectfully requested.

Rejection of Claims 22, 23, and 25 Under 35 USC §103 in View of U.S. Patent No. 5,348,945 (Berberian et al., "the '945 Patent") in View of Hsu:

This rejection is respectfully traversed.

As amended Claim 22 recites a pharmaceutical composition comprising an immunoglobulin heavy chain binding protein "designated BiP(GRP78)." This is a distinctly different protein from the hsp70 protein disclosed in the primary reference to Berberian et al.

Specifically, note that hsp70 proteins are explicitly described in the Berberian et al. patent as being "**the most highly conserved** member of the hsp family" (emphasis added). See Berberian et al., col. 4, lines 60-65. The BiP(GRP78) proteins are also highly conserved across species. But, BiP(GRP78) is a different protein from hsp70. The BiP(GRP78) protein is translated from a unique gene, a gene which is not

the gene for hsp70. In short, the hsp70 protein referred to in Berberian et al. is not the same protein as the BiP(GRP78) protein described in the present claims.

The **combination** of Berberian et al. with Hsu et al. does not cure the deficiencies in the primary reference because the Hsu et al. reference is limited entirely to a description of expressing BiP in a baculovirus system using insect cells, and using that BiP so produced to improve the functionality of the baculovirus system itself. This Hsu reference has nothing at all to do with using BiP proteins to treat rheumatoid arthritis in man or to treat any type of disease state. Whereas the primary reference does address treating a disease state, Hsu is concerned solely with improving functional antibody production in a baculovirus expression system.

Thus, there is no motivation in the first instance for combining Berberian et al. with the Hsu et al. reference. Whereas Berberian et al. uses the hsp70 proteins as an active ingredient in an pharmaceutical composition, Hsu et al. uses the BiP chaperone protein as a means to improve post-translation modification of antibodies produced in a baculovirus system. Hsu et al. is not interested in the BiP protein as an end in itself, or as a pharmceutically active ingredient. Hsu's sole interest in using BiP is to co-express it with the desired antibody gene, in the hope that the presence of the co-expressed BiP will result in proper post-translational modification **of the desired antibody**. Hsu et al. are interested in the antibody as the final product, not the BiP. Thus, there is no motivation, within the references themselves to combine the two references.

Even if the combination is made, it does not teach or fairly suggest the present invention. **Combining** Berberian et al. with Hsu et al. teaches using the baculovirus system as taught by Hsu et al. to co-express Berberian's hsp70 protein along with BiP. The active ingredient used would then be Berberian's co-expressed (and hopefully properly post-translationally modified) **hsp70 protein, not the co-expressed BiP**.

This is clear from the combined teaching of Berberian et al. and Hsu et al. Berberian teaches using hsp70 as an active ingredient. Hsu et al. teaches using a BiP protein solely **t impr ve the pr duction of an active ingredient** using a baculovirus

system. Thus, combining the two yields a method wherein Hsu's baculovirus system (wherein a BiP is co-expressed with the protein of interest) is used to produce the hsp70 protein of Berberian et al. In no fashion do the combined reference teach or fairly suggest that the BiP as descibed by Hsu et al. is to be used as the active ingredient in a pharmaceutical composition.

Thus, applicants respectfully submit that this reject is improper. Withdrawal of the same is respectfully requested.

CONCLUSION

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 09/806,955 Group Art Unit: 1644

Filed: 07/11/2001 Examiner: Jamroz, M.

Applicants: Panayi et al. Attorney Docket No.: 78104.023

Title: **TREATMENT OF INFLAMMATORY DISEASE**

"MARKED UP" CLAIMS AS AMENDED, 37 CFR §1.121(c)(1)(ii)

18. **[AMENDED] [Recombinant]** **A recombinant** immunoglobulin heavy chain binding protein **designated BiP(GRP78) and having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2**.

19. [CANCEL] ~~The recombinant immunoglobulin heavy chain binding protein of Claim 18, having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2~~.

20. [CANCEL] ~~An isolated DNA molecule having or containing a nucleotide sequence as shown in SEQ. ID. NO: 3.~~

21. [CANCEL] ~~A recombinant vector comprising a DNA sequence as shown in SEQ. ID. NO: 3.~~

22. **[AMENDED]** A pharmaceutical composition for the treatment of [inflammation] **rheumatoid arthritis** in mammals, including humans, the composition comprising an [anti-inflammatory-effective] **anti-rheumatoid-arthritic** amount of **an isolated** immunoglobulin heavy chain binding protein **designated BiP(GRP78)** or a **[peptide derived therefrom] fragment thereof**, in combination with a pharmaceutically-suitable carrier.

23. **[AMENDED]** The pharmaceutical composition of Claim 22, wherein the immunoglobulin heavy chain binding protein is **a** recombinant immunoglobulin heavy chain binding protein.

24. The pharmaceutical composition of Claim 22, wherein the immunoglobulin heavy chain binding protein has an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2.

25. [CANCEL] ~~The pharmaceutical composition of Claim 22, which is a composition for the treatment of rheumatoid arthritis.~~

26. [CANCEL] ~~A pharmaceutical composition for the treatment of inflammation in mammals, including humans, the composition comprising an anti-inflammatory-effective amount of a DNA encoding immunoglobulin heavy chain binding protein or an anti-inflammatory fragment derived therefrom, in combination with a pharmaceutically-suitable carrier.~~

27. [CANCEL] ~~The pharmaceutical composition of Claim 26, wherein the DNA encoding immunoglobulin heavy chain binding protein is recombinant DNA.~~

28. [CANCEL] ~~The pharmaceutical composition of Claim 26, wherein the DNA encoding immunoglobulin heavy chain binding protein has a nucleotide sequence as shown in SEQ. ID. NO: 3.~~

29. [CANCEL] ~~The pharmaceutical composition of Claim 26, which is a composition for the treatment of rheumatoid arthritis.~~

30. **[AMENDED]** A method for treating **[inflammation]** **rheumatoid arthritis** in a mammalian subject in need thereof, including a human subject, the method comprising administering to the subject an **anti-rheumatoid-arthritic** amount of immunoglobulin heavy chain binding protein **designated BiP(GRP78)** or a **[peptide derived therefrom] fragment thereof[, the amount being effective to ameliorate in the subject]**.

31. [CANCEL] ~~The method of Claim 30, which is a method of treating rheumatoid arthritis.~~

32. **[AMENDED]** The method of Claim 30, wherein **a** recombinant immunoglobulin heavy chain binding protein is administered to the subject.

33. **[AMENDED]** The method of Claim 32, wherein **a** recombinant immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID NO: 2 is administered to the subject.

34. The method of Claim 30, wherein the immunoglobulin heavy chain binding protein is administered orally, nasally, subcutaneously, or intravenously.

35. [CANCEL] ~~A method for treating inflammation in a mammalian subject in need thereof, including a human subject, the method comprising administering to the subject an amount of a DNA encoding immunoglobulin~~

~~heavy chain binding protein or a fragment thereof, the amount being effective to ameliorate inflammation in the subject~~.

36. [CANCEL] ~~The method of Claim 35, which is a method of treating rheumatoid arthritis.~~

37. [CANCEL] ~~The method of Claim 35, wherein recombinant DNA encoding immunoglobulin heavy chain binding protein is administered to the subject~~.

38. [CANCEL] ~~The method of Claim 37, wherein recombinant DNA having a nucleotide sequence as shown in SEQ. ID. NO: 3 is administered to the subject~~.

39. [CANCEL] ~~The method of Claim 35, wherein the DNA is administered orally, nasally, subcutaneously, or intravenously~~.

40. **[AMENDED]** A method for diagnosing the presence of rheumatoid arthritis in a mammalian subject, including a human subject, the method comprising contacting a bodily fluid from the subject selected from the group consisting of whole blood, blood plasma, blood serum, saliva, mucus, synovial fluid, and cerebrospinal fluid, to immunoglobulin heavy chain binding protein **designated BiP(GRP78)** or a **[peptide derived therefrom] fragment thereof**, and then ascertaining the presence or absence of anti-immunoglobulin heavy chain binding protein antibodies in the bodily fluid tested, the presence of antibodies indicating the presence of rheumatoid arthritis in the subject.

41. **[AMENDED]** The method of Claim 40, wherein the bodily fluid is contacted with **a** recombinant immunoglobulin heavy chain binding protein

42. **[AMENDED]** The method of Claim 40, wherein the bodily fluid is contacted with **[Immunoglobulin] an immunoglobulin** heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2.

43. **[AMENDED]** The method of Claim 40, wherein the presence of **an** anti-immunoglobulin heavy chain binding protein antibodies is ascertained using an enzyme-linked immunosorbent assay (ELISA) incorporating **an** immunoglobulin heavy chain binding protein or a **[peptide derived therefrom] fragment thereof.**

44. **[AMENDED]** A kit for diagnosing the presence of rheumatoid arthritis in a mammalian subject, including a human subject, the kit comprising:

an amount of an isolated immunoglobulin heavy chain binding protein designated BiP(GRP78) or a [peptide derived therefrom] fragment thereof, disposed in a suitable container.

45. The kit of Claim 44, further comprising instructions for use of the kit.

46. [AMENDED] The kit of Claim 44, comprising a recombinant immunoglobulin heavy chain binding protein or a [peptide derived therefrom] fragment thereof.

47. [AMENDED] The kit of Claim 44, comprising immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2 or a fragment thereof.

48. [AMENDED] The kit of Claim 44, comprising an enzyme-linked immunosorbent assay that incorporates the immunoglobulin heavy chain binding protein or [a] the fragment thereof [peptide derived therefrom].

49. [AMENDED] The kit of Claim 48, comprising a recombinant immunoglobulin heavy chain binding protein or a [peptide derived therefrom] fragment thereof.

50. [AMENDED] The kit of Claim 48, comprising a recombinant immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2 or a fragment thereof.

51. [AMENDED] The kit of Claim 44, comprising a Western Blot assay that incorporates the immunoglobulin heavy chain binding protein or [a peptide derived therefrom] the fragment thereof.

52. [AMENDED] The kit of Claim 51, comprising a recombinant immunoglobulin heavy chain binding protein or a [peptide derived therefrom] fragment thereof.

53. [AMENDED] The kit of Claim 51, comprising a recombinant immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2 or a fragment thereof.

54. [NEW] An isolated polypeptide having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 09/806,935 Group Art Unit: 1644

Filed: 07/11/2001 Examiner: Jamroz, M.

Applicants: Panayi et al Attorney Docket No.: 78104.023

Title: **TREATMENT OF INFLAMMATORY DISEASE**

"MARKED UP" SPECIFICATION PARAGRAPHS, 37 CFR §1.121(b)(1)(iii)

At page 2, please delete the first paragraph (spanning lines 1-12), and insert in its place the following paragraph:

-- We have now obtained and identified the correct RA autoantigen and this discovery leads to the development of prognostic and diagnostic tests for this disease and specific therapy. We have isolated and sequenced the **native** DNA for this **[protein] autoantigen**. We have also cloned and expressed this DNA. The amino acid and DNA sequences are novel and are shown in the Sequence **List [Listings appended to this specification]**. The amino acid sequences of the BiP protein are given as **[sequence listings in]** two versions **[SE1 and SE2 either of which], SEQ. ID. NO: 1 (which includes a histidine tag) and SEQ. ID. NO: 2 (which lacks the histidine tag). Either SEQ. ID. NO: 1 and/or SEQ. ID. NO: 2** may be used as a test reagent in accordance with the present invention. The cDNA for **[SE1 is given as Sequence listing SE3] SEQ. ID. NO: 1 is disclosed in SEQ. ID. NO: 3**. This sequence **(SEQ. ID. NO: 3)** has been deposited with GENBANK under Accession No. AF 188611. A comparison of this sequence with that of GENBANK Accession No. X 87949 is provided hereinafter. --

At page 7, please delete the third full paragraph (spanning lines 5-7), and insert in its place the following paragraph:

-- NQLTSNPENTVFDAK **(SEQ. ID. NO: 6)** 82-96
SDIDEIVLVGGSTR **(SEQ. ID. NO: 7)** 353-366
TWNDPSVQQDIK **(SEQ. ID. NO: 8)** 107-113 --

At page 7, please delete the fourth full paragraph (spanning lines 8-10), and insert in its place the following paragraph:

-- Identified human protein: GR 78[:].
[Kd] Glucose-regulated [glucose related] protein precursor: [(]GRP78[)].
Immunoglobulin heavy chain binding protein: [(]BIP[)]. --

At page 8, please delete the third full paragraph (spanning lines 17-20), and insert in its place the following paragraph:

-- Bip Forward Primer:
5'-TATACATATGGAGGAGGACAAGAAGGAGGACG-3' **[32mer]** **(SEQ. ID NO: 4)**
Bip Reverse Primer
5'-CCACCTCGAGTTCTGCTGTATCCTCTTCACCA-3' **[32mer]** **(SEQ. ID. NO: 5)** --

Please delete the paragraph spanning page 14, line 21, to page 15, line 5, and insert in its place the following paragraph:

-- Despite the failure to induce arthritis by immunising animals with p78, we investigated whether DBA/1 mice during the course of **[c llagen (CIA) or pristane**

(PIA) induced arthritis] <u>CIA or PIA</u> developed antibodies to p78 **[(Figure 4)]**. <u>The results are depicted in Fig. 3.</u> Mice developed serum anti-p78 antibodies at the onset of **[collagen arthritis]** <u>CIA</u> ($O.D._{405}$ 0.189 ± 0.042, m $\pm$ sem) and **[pristane induced arthritis]** <u>PIA</u> (0.504 ± 0.074) when compared to pre-bleed sera (0.070 ± 0.019; $p <$ versus CIA and $p <$ versus PIA, respectively). Furthermore, the concentration of these antibodies was significantly higher in the PIA mice as compared to the CIA mice **[(p)]**. There were 14 mice in each group. --

Please delete the paragraph spanning page 15, lines 7-20, and insert in its place the following paragraph:

-- The presence of antibodies to p78 in the sera of mice with CIA or PIA suggested that manipulating the immune response to p78 might prevent the subsequent development of CIA by a bystander phenomenon. HLA-$DR1^{+/+}$ transgenic mice were injected intravenously with 1 mg of p78 prior to immunisation with type II collagen in CFA one week later (Table 2). Whereas 83% of animals had 46% of their limbs involved with arthritis at 8 weeks when **[pretreated]** <u>pre-treated</u> with saline, only 10% of animals had only 3% of their limbs involved with arthritis in the group previously given intravenous p78. These differences are highly significant ($p \leq 0.008$ and $p \leq 0.0001$). Table 2 also shows that there was a significant reduction in **[anticollagen]** <u>anti-collagen</u> antibodies in the p78 pre-treated animals to one third the level in the controls. The reduction was equal in the IgG1 and IgG2 isotypes (Table 3). The histology of the joints of these animals **[(Figure 6)]** confirmed the clinical findings in that there was no synovitis in the joints of pre-treated mice. --